REMARKS

I. Status of the Claims

Claims 7-16 are currently pending. Applicants first amend the claims in order to separate the components of the "infectious disease such as leprosy" into two separate claims. The phrase "such as leprosy" is removed from claim 10 and "leprosy" is recited in new claim 16. Since this amendment merely rearranges the already claimed subject matter, it does not change the scope of the claims, require a further search of the art, or introduce new matter.

Applicants also amend claims 7 and 8 to replace "caused by" with "characterized by" merely for further clarification and to speed prosecution. This amendment is supported by the specification as a whole, for example, at page 1, line 34, and surrounding text. This amendment also does not narrow the scope of the claims, require a further search of the art, or introduce new matter.

Applicants respectfully request the entry of the amendments.

II. Claims 7 and 10-16 Are Enabled

The Office first contends that claims 7 and 10-15 are not enabled according to 35 U.S.C. § 112, first paragraph. (Office Action at pages 2-3.) Applicants respectfully traverse this rejection.

First, the Office contends that the specification and prior art do not enable claims reciting "prophylaxis" of disorders. Yet, the Office merely asserts that model data is insufficient to show that "active antithrombin III" treatment would prevent recurrence of symptoms upon challenge. (Office Action at page 2.) Such a conclusory rejection is not a *prima facie* case of non-enablement. Instead, a *prima facie* case requires evidence

from the art or fact-based scientific reasoning. *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001); *In re Lee*, 61 U.S.P.Q.2d 1430, 1433-5 (Fed. Cir. 2002). Moreover, enablement is judged from the point of view of one of ordinary skill in the art, not from the point of view of the Office. Therefore, the Office bears the burden to explain, using sound, scientific reasoning supported by evidence from the literature, why one of ordinary skill in the art would allegedly believe that "prophylaxis" is not enabled.

Despite these deficiencies, the instant claims reciting "prophylaxis" are enabled. Pharmaceutical methods need not be ultimately successful in human trials to be patentable. In fact, an applicant need only show that the success of the method is *credible* to one of ordinary skill in the art. M.P.E.P. §§ 2164.02 and 2107.01(III).

To meet this standard, all that is necessary is a reasonable correlation between the claims and the *in vitro* or *in vivo* model data in the specification and prior art. M.P.E.P. §§ 2164.02 and 2107.01(III); *Cross v. Iizuka*, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Brana*, 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995). A rigorous or exact correlation is not required. *Cross v. Iizuka*, 224 U.S.P.Q. 739 (Fed. Cir. 1985). Instead, the standard recognizes that lengthy or complex experimentation may still be needed before a pharmaceutical method may be useful. M.P.E.P. § 2164.01. Indeed, the Federal Circuit has explained that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a model has made a significant contribution to the art, even if the compound later turns out not to be useful in human treatment. *Brana*, 34 U.S.P.Q.2d at 1442.

In this case, prophylactic treatment simply refers to treatment given to an individual suspected of suffering from, or at risk of suffering from, angiogenesis or

arteriogenesis. Further, the same general factors are involved at beginning and later stages of angiogenesis. For instance, page 443 of Abdulkadir et al. comments that tissue factor can both enhance the growth as well as the initiation of angiogenesis in cancer. (Abdulkadir et al., *Human Pathology*, 31: 443-7 (2000); of record.) Therefore, one of ordinary skill in the art would reasonably conclude that a drug that inhibits cell proliferation would be credibly useful if given to patients known to be suffering from angiogenesis or arteriogenesis as well as to those at risk for these conditions.

In summary, because the Office has not raised a *prima facie* case of lack of enablement, and because Applicants' specification and the art demonstrates a correlation between Applicants' findings and the claimed subject matter, Applicants request the withdrawal of this rejection.

The Office also rejects claims 7 and 10-15 due to the phrase "*caused by* angiogenesis or arteriogenesis." This rejection is moot in light of Applicants' claim amendments.

III. Claim 10 Is Definite

The Office rejects claim 10 under 35 U.S.C. § 112, second paragraph, due to the phrase "infectious disease such as leprosy." (Office Action at page 4.)

This rejection is moot as Applicants have separated the subject matter recited in that phrase into two separate claims. Claim 10 now recites "infectious disease," while new claim 16 recites that the "infectious disease" is "leprosy." Thus, Applicants request the withdrawal of this rejection.

IV. Claims 7-16 Are Novel and Nonobvious over Canadian Patent Application No. 2,315,558

The Office rejects claim 7-15, asserting that they are either anticipated or obvious over Canadian patent application 2,315,558 to an overlapping inventive entity. (Office Action at pages 4-5.) Applicants submit herewith a certified translation of German priority application 101 02 048.1, filed January 17, 2001. Because the Canadian patent application published after the German priority application was filed, it does not qualify as prior art against the instant application. Thus, Applicants request the withdrawal of this rejection.

V. Claims 8-16 Are Novel and Nonobvious over O'Reilly

The Office also rejects claims 8-15 as allegedly anticipated or obvious in light of two publications by O'Reilly et al. ("O'Reilly"; U.S. Patent No. 6,607,724 B2 or U.S. Publication No. 2002/0076413 A1). (Office Action at pages 5-6.) O'Reilly patent and published application represent the same U.S. patent application. Therefore, their disclosures are nearly identical. Like the Office, Applicants refer only to the published application. But Applicants' comments apply equally to the issued patent.

Applicants traverse this rejection because O'Reilly's patent and published application do not teach or suggest all of the elements of Applicants' claims, as required for anticipation, and because this rejection fails all three prongs of the test of obviousness.

In order to anticipate a claim, a single publication must teach, either expressly or inherently, each and every element of the claim, in as complete detail as contained within the claim. M.P.E.P. § 2131; *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2

U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). O'Reilly fails this test. Thus, O'Reilly's published application and patent cannot anticipate any of claims 8-15.

Instant claims 7 and 8, from which all of claims 9-16 depend, require "administering ***active*** antithrombin III to a patient in need thereof." In contrast, O'Reilly does not teach or suggest administering "active antithrombin III." In fact, it teaches that one ***should not*** administer "active antithrombin III."

For example, antithrombin III (AT3) is a serine protease inhibitor, or "serpin" protein, that can inactivate thrombin and other enzymes. (O'Reilly published application at [0006].) Thus, inactive AT3 lacks serine protease activity. First, O'Reilly distinguishes between active and inactive forms of AT3. O'Reilly comments that the "active" form of ATIII "is designated the S (stressed) form (S-AT3). S-AT3 forms a tight binding complex with thrombin . . . and other enzymes. . ." (*Id.*) O'Reilly also points out at [0041] and [0042] that both the R (relaxed) and L (latent or locked) forms of AT3 are ***not active***. For example, it states that R-AT3 "is no longer active as an inhibitor of serine proteases" and that the L-AT3 forms "are structurally similar to the R-AT3 form . . . resulting in a more stable conformation that is no longer active as a serine protease inhibitor." Thus, O'Reilly distinguishes "active" or S-AT3 from all of the other forms of AT3 it mentions, including R (relaxed) and L (latent or locked) forms.

Both the R and L forms are generated by specific laboratory manipulations such as elastase cleavage or guanidine chloride denaturation of the S-AT3 form. (O'Reilly at [0007] and [0008].) This provides another, more practical way of distinguishing these forms.

Second, O'Reilly teaches that inactive or "R-AT3 has potent anti-angiogenic and anti-tumor activity ***which is not found in S-AT3***." (O'Reilly at [0043], emphasis added.) In other words, it teaches that active, S-AT3 is not anti-angiogenic. Specifically, in Example 3, at [0088] to [0090], O'Reilly comments that "intact native (S-AT3) had no significant effect on non-endothelial cells and only marginally inhibited capillary endothelial cells at doses in excess of 10 µg/mL." (O'Reilly at [0089].) Such results are depicted in O'Reilly's Figures 3-5, in which "active" or S-AT3 had virtually no effect on capillary endothelial cell proliferation or on tumor volume. Thus, these statements and results demonstrate that O'Reilly does not teach or suggest administering "active antithrombin III" to treat "a disorder characterized by angiogenesis or arteriogenesis" as Applicants' claim.

For similar reasons, O'Reilly also fails to render the instant claims obvious. There are three distinct requirements for a *prima facie* case of obviousness.[1] First, the references must teach or suggest every claim element. M.P.E.P. §§ 2142 and 2143.03. As just described, O'Reilly fails this test because it does not suggest using "active antithrombin III" in a medical treatment for "angiogenesis or arteriogenesis," as Applicants' claim.

Second, there must be a motivation to modify the teachings of the cited references. M.P.E.P. §§ 2143 and 2143.01. That motivation must come from the references themselves or from the knowledge generally available to one of ordinary skill in the art; not from the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir.

[1] Again, while the Office cites two documents by O'Reilly, their disclosures are virtually identical. Hence, they do not teach any more in combination than each teaches individually.

1991); M.P.E.P. § 2142. Further, the mere fact that the references *can* be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The modification or combination must be *desirable*, not merely feasible. M.P.E.P. § 2143.01; *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587-8 (Fed. Cir. 2000).

O'Reilly also fails this test. O'Reilly does not motivate one of ordinary skill in the art to use "active antithrombin III" because its data and working examples show that the "active" S-AT3 forms had virtually no effect on tumor volume or capillary endothelial cell proliferation. In contrast, the inactive R and L forms successfully inhibited capillary endothelial cell proliferation and shrunk tumors. (See O'Reilly at Example 3 and Figures 3-5, for example.) For the same reason, O'Reilly also fails to demonstrate a reasonable expectation of success, the third requirement for obviousness.

In fact, O'Reilly as a whole teaches away from Applicants' claims because it repeatedly concludes that the S-AT3 "active" form is not useful in combating angiogenesis. Courts have long pointed out that teaching away is "strong evidence of unobviousness." *See, e.g., In re Hedges,* 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986).

Finally, a *prima facie* case of either anticipation or obviousness requires substantial evidence or scientific reasoning firmly grounded in fact. *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). The Federal Circuit has emphasized that a *prima facie* case of obviousness, for example, must include a thorough explanation, on the record, of why the Office believes there is motivation to modify or combine the references it cites. *See Lee* at 1433-5. In contrast, the Office here merely asserts that O'Reilly discloses an "active" form of AT3.

(Office Action at page 6.) But the Office does not consider what O'Reilly actually teaches about that form. The Office provides no explanation of why it believes there is motivation to modify O'Reilly or a reasonable expectation of success in doing so. Thus, the Office has not set forth a *prima facie* case.

For all of the above reasons, Applicants' claims are novel and nonobvious. Applicants request the withdrawal of these rejections.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not found herewith to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: April 29, 2004

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